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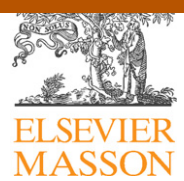

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CLINICAL RESEARCH

Echocardiography to predict adverse cardiac and vascular events in patients with severe chronic kidney disease (stage 4): A prospective study

Prédiction des évènements cardiovasculaires chez l'insuffisant rénal chronique sévère (stade 4) par échocardiographie

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KEYWORDS
Chronic kidney disease;
Cardiovascular disease;
Echocardiography

Summary
Background. — Cardiovascular disease is the primary cause of mortality and morbidity among patients with chronic kidney disease.
Aims. — To investigate whether echocardiography can predict the occurrence of major cardiovascular events in patients with severe chronic kidney disease.
Patients. — Patients with stable stage 4 chronic kidney disease (estimated glomerular filtration rate 15—29 mL/min/1.73 m^2) and followed in the nephrology department were included. Clinical, biological, electrocardiographic and echocardiographic data were recorded. Endpoint was defined as fatal or non-fatal cardiovascular event (acute coronary syndrome, acute heart failure, stroke, sustained ventricular arrhythmias, arterial thrombotic events and death).
Results. — We included 71 patients (46 men); mean age 72 ± 14 years. Mean glomerular filtration rate was 21.9 ± 4.8 mL/min/1.73 m^2. Over a mean follow-up of 258 ± 30 days, 18 (25%) patients reached endpoint (death in 7/18). Male sex, blood urea, atrial fibrillation, Sokolow index, left atrial size, pulmonary arterial pressure, indexed left ventricular mass and protodiastolic peak velocity of transmitral Doppler flow were significantly higher whereas left ventricular ejection

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MACE, major acute cardiac and vascular events; MDRD, Modification of Diet in Renal Disease; OR, odds ratio; ULN, upper limit of normal.

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fraction was significantly lower in these patients. By multivariable analysis, blood urea and left ventricular ejection fraction remained predictive of major cardiovascular event with odds ratios of 1.10 (95% confidence interval 1.02—1.18) and 0.93 (95% confidence interval 0.89—0.97), respectively. The negative predictive value was 95% when left ventricular ejection fraction was > 50% with blood urea < 15 mmol/L.
Conclusion. — Patients with stage 4 chronic kidney disease are at high risk of major cardiovascular events and death. Echocardiographic evaluation is effective in identifying patients at highest risk of adverse cardiac events.

MOTS CLÉS
Insuffisance rénale chronique ;
Maladies cardiovasculaires ;
Échocardiographie

Résumé
Contexte. — Les maladies cardiovasculaires sont la première cause de morbimortalité en cas d'insuffisance rénale chronique.
Objectif. — Déterminer si l'échographie pouvait prédire la survenue d'événements indésirables cardiovasculaires majeurs en cas d'insuffisance rénale chronique sévère.
Patients. — Les patients avec insuffisance rénale chronique sévère (stade 4, débit de filtration glomérulaire entre 15 et 29 mL/min/1,73 m^2) stable suivis en néphrologie ont été inclus. Les données cliniques, biologiques, électrocardiographiques et échographiques ont été enregistrées. Le critère d'évaluation a été défini par la survenue d'événements cardiovasculaires mortels ou non (syndrome coronarien aigu, insuffisance cardiaque aiguë, accident vasculaire cérébral, arythmie ventriculaire soutenue, événements thrombotiques artériels et décès).
Résultats. — Nous avons inclus 71 patients (46 hommes), d'âge moyen 72 ± 14 ans. Le débit de filtration glomérulaire moyen était de 21,9 ± 4,8 mL/min/1,73 m^2. Au cours d'un suivi moyen de 258 ± 30 jours, 18 patients (25 %) ont atteint le critère d'évaluation (dont sept décès). Le sexe masculin, l'urémie, la fibrillation atriale, l'indice de Sokolow, la taille de l'oreillette gauche, la pression artérielle pulmonaire, la masse ventriculaire gauche indexée et le pic protodiastolique du flux doppler transmitral étaient significativement plus élevés alors que la fraction d'éjection ventriculaire gauche significativement plus faible chez ces patients. En analyse multivariée, l'urémie et la fraction d'éjection ventriculaire gauche restaient prédictives d'évènement (OR 1,10 (IC 95 % [1,02, 1,18]) et 0,93 IC 95 % [0,89, 0,97], respectivement). La valeur prédictive négative était de 95 % lorsque la fraction d'éjection ventriculaire gauche était supérieure à 50 % avec une urémie inférieure à 15 mmol/L.
Conclusion. — La morbimortalité cardiovasculaire est élevée en cas d'insuffisance rénale chronique sévère. L'évaluation échocardiographique est efficace pour identifier les patients à haut risque.

Background

A strong association exists between chronic kidney disease (CKD) and cardiovascular disease (CVD), with an increase in CVD observed with declining glomerular filtration rate [1—5]. Indeed, CVD is the main cause of morbidity and mortality in CKD patients. In a study conducted by Go et al. [2], with more than one million patients classified into subgroups according to CKD stage, annual mortality and cardiovascular morbidity were 11.4% and 21.8%, respectively, in stage 4 patients. Cardiovascular risk is, however, difficult to assess in patients with stage 4 or stage 5 CKD, and risk scores, such as those derived from the Framingham study, are not accurate in the CKD population [6].

In patients undergoing dialysis, the value of echocardiography to predict cardiovascular events and death has been reported [7—11]. However, data are lacking from patients with stage 4 CKD to help identify those at higher risk of cardiovascular morbidity [12,13]. Using the modification of diet in renal disease (MDRD) formula [14], 0.5% of the adult participants in the NHANES 1999—2006 cohort had an estimated glomerular filtration rate < 30 mL/min/1.73 m^2 [15]. Few studies have been conducted in these patients — mainly evaluations of subgroups. In addition, randomized clinical trials usually exclude patients with severe CKD [16,17]. Unlike patients undergoing dialysis, stage 4 CKD patients are not generally considered as a specific population in the cardiology setting and no specific echocardiographic data from these patients have been reported [18]. However, earlier detection of patients at high risk of cardiovascular complications could help physicians to adapt therapy and follow-up accordingly, thereby potentially delaying the occurrence of adverse cardiac events or the initiation of renal replacement therapy.

The aim of this prospective cohort study was to identify echocardiographic variables that may predict cardiac and vascular complications in patients with stage 4 CKD and to describe cardiovascular status, echocardiographic data and occurrence of cardiac and vascular adverse events.

Patients

Inclusion criteria and study population

In our centre, patients with stable stage 4 CKD are seen in consultation every 3 months for regular follow-up. All prospective patients attending these consultations over a period of 5 months with stable stage 4 CKD and an estimated glomerular filtration rate between 15 and 30 mL/min/1.73 m^2 according to the MDRD formula were considered eligible for inclusion. Patients were included during their consultation if they gave informed consent. Data were collected during standard care. Exclusion criteria were as follows: acute renal failure with serum creatinine increase of 50% from baseline level in the 3 previous months; CKD diagnosed < 3 months previously; and history of transplantation.

Data collection

Cardiovascular history, traditional risk factors for CVD (hypertension, diabetes mellitus, current smoking, hyperlipidaemia, being overweight and family history of vascular disease), the cause of nephropathy and body surface area were recorded. In all patients, heart rate and arterial blood pressure were measured and a 12-lead electrocardiogram was performed at inclusion.

Transthoracic echocardiography was performed in all participants, using ACUSON SEQUOIA C256 equipment (Siemens, Munich, Germany) with data obtained in digital format and stored for off-line analysis. Two independent operators interpreted the echocardiography blind with respect to clinical data, according to the American Society of Echocardiography recommendations [19], with an average of at least three successive measurements (five if atrial fibrillation [AF] was present). Left ventricular ejection fraction (LVEF) (Simpson's biplane method), left ventricular mass (cubes method according to American Society of Echocardiography convention [20]), left atrium surface area (four-chamber planimetry) and pulmonary arterial pressures (derived from tricuspid and/or pulmonary regurgitation flow) were measured. Right atrial pressure was estimated by inferior vena cava diameter and the presence of inspiratory collapse. Inferior vena cava diameter < 2 cm with collapse > 50% during inspiration and > 2 cm with collapse < 50% suggested right atrial pressures of 5 and 15 mmHg, respectively; intermediate cases suggested a right atrial pressure of 10 mmHg. Left ventricular filling pattern was also collected with transmitral Doppler flow analysis and the measurements of E mitral protodiastolic peak velocity, E mitral deceleration time, A mitral end-diastolic peak velocity, A mitral duration, isovolumetric relaxation time and Doppler tissue imaging on the lateral side of mitral annulus (early peak velocity). Valvular diseases were quantified using the reference methods. Left ventricular mass and aortic valve area were indexed to body surface area.

LVEF < 50%, indexed left ventricular mass > 95 g/m^2 for women and > 115 g/m^2 for men, left atrial surface area > 20 cm^2 and systolic pulmonary artery pressure > 40 mmHg were considered abnormal. Biological variables were also recorded (serum creatinine, blood urea, calcium, phosphate, protein, albumin, haemoglobin, intact parathyroid hormone, glycated haemoglobin, C-reactive protein and 24-hour proteinuria).

During the follow-up period, all-cause death and cardiovascular death were recorded. A composite endpoint of major acute cardiac and vascular events (MACE) was defined as cardiovascular death, non-fatal cardiovascular events, acute coronary syndromes (with or without ST-segment elevation), ischaemic stroke, acute arterial ischaemia, acute heart failure or sustained ventricular arrhythmias. In addition, cardiovascular and all-cause admissions, need for dialysis, kidney transplant and death were recorded.

The study was designed to follow patients up to 1 year after inclusion.

Statistical analysis

Quantitative data are presented as mean ± standard deviation and qualitative data as number and percentage. Event-free survival analysis was performed using Kaplan-Meier survival analysis and compared using the log-rank test. Variables that differed significantly between groups by univariate analysis were included in the multivariable analysis, using an ascending stepwise Cox proportional hazards model. We planned to perform the analysis in two stages, due to the small number of expected events. Firstly, echocardiographic and non-echocardiographic variables would be analysed separately and the independent variables would subsequently be included in the final multivariable analysis combining both echocardiographic and non-echocardiographic variables. A post hoc analysis of the predictive value of the combination of independent predictors using established cut-off values was also performed (50% for LVEF [21] and 2 × upper limit of normal [ULN] for urea). A Kaplan-Meier curve was drawn to visualize the prognostic value of independent variables significantly associated with MACE occurrence and of their combination. All analyses were performed using SPSS 19 software (IBM, SPSS Inc. Chicago, IL, USA) and for all tests a P value < 0.05 was considered significant.

Results

Study population and MACE

We prospectively screened 78 patients, of whom 71 were included (46 men and 25 women). Six patients did not give consent to participate and one was excluded after echocardiography, because of severe aortic valve stenosis requiring surgery. All but one of the 71 included patients were white, mean age was 72 ± 14 years (range 27—95) and 10 patients had an arteriovenous fistula.

The baseline characteristics of the study population are displayed in Table 1. Only four patients had no risk factors, while 15, 22, 15 and 15 patients had one, two, three and four or more risk factors, respectively. Thirty-one patients had previous atheromatous disease with a history of at least one of the following: acute coronary syndrome (n = 15), stroke (n = 9), peripheral arteriopathy (n = 16) and renal artery stenosis (n = 3). The primary causes of CKD were nephrosclerosis (41%), diabetic nephropathy (31%), tubulointerstitial nephritis (10%), chronic glomerulonephritis (8%) and other

Table 1 Baseline characteristics of the study population.

	All ($n=71$)	Event-free ($n=53$)	Event ($n=18$)	P
Men	46 (65)	30 (57)	16 (89)	0.01
Age (years)	72 ± 14	70.7 ± 14.5	76 ± 11.5	0.17
Cardiovascular history				
Acute heart failure	14 (20)	7 (13)	7 (39)	0.02
Atheromatous disease	31 (44)	20 (38)	11 (61)	0.06
Cardiovascular risk factors				
Hypertension	58 (82)	41 (77)	17 (94)	0.12
Diabetes mellitus	25 (35)	18 (34)	7 (39)	0.79
Dyslipidaemia	30 (42)	24 (45)	6 (33)	0.71
BMI > 25 kg/m^2	40 (56)	31 (58)	9 (50)	0.44
Smoking (current/stopped < 3 years)	10 (14)	8 (15)	2 (11)	0.29
Family history of early vascular disease	6 (9)	4 (8)	2 (11)	0.49
Haemodynamic variables				
Systolic blood pressure (mmHg)	139 ± 19	140 ± 17	137 ± 22	0.24
Diastolic blood pressure (mmHg)	74 ± 9	74 ± 10	72 ± 7	0.28
Heart rate (beat/min)	69 ± 12	70 ± 12	68 ± 10	0.81
Medical therapy				
ACEI or ARB	55 (78)	40 (76)	15 (83)	0.44
Antiplatelet agent	29 (41)	18 (34)	11 (61)	0.11
Statins	17 (24)	11 (21)	6 (33)	0.54
Diuretic	50 (70)	34 (64)	16 (89)	0.002
Beta-blocker	29 (41)	17 (32)	11 (61)	0.049
Biological variables				
Creatinine (μmol/L)	281 ± 122	276 ± 127	295 ± 107	0.58
eGFR (MDRD mL/min/1.73 m^2)	21.9 ± 4.8	22.4 ± 4.5	20.5 ± 5.2	0.38
Blood urea (mmol/L)	18.7 ± 7.0	16.9 ± 6.1	23.4 ± 7.2	0.001
Blood urea/creatinine	69 ± 19	65 ± 18	81 ± 18	0.001
Proteinuria (g/24 h)	1.2 ± 1.6	1.1 ± 1.4	1.4 ± 2.1	0.37
Albumin (g/L)	40 ± 5	40 ± 24	38 ± 4	0.13
Calcium (mmol/L)	2.31 ± 0.16	2.33 ± 0.15	2.27 ± 0.17	0.21
Phosphate (mmol/L)	1.34 ± 0.31	1.32 ± 0.30	1.40 ± 0.32	0.33
iPTH (pg/mL)	200 ± 236	181 ± 171	234 ± 326	0.53
HbA1c (%)	6.5 ± 1.5	6.20 ± 1.52	6.65 ± 1.20	0.40
Haemoglobin (g/L)	120 ±12	121 ± 12	118 ± 14	0.48
CRP > 3 mg/L	34 (48)	17 (32)	6 (33)	0.25
Atrial fibrillation	10 (14)	2 (4)	8 (44)	< 0.001
Sokolow index (mm)	20 ± 7	19 ± 7	25 ± 9	0.009

Data are presented as mean ± standard deviation or number (%). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; BMI: body mass index; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; iPTH: intact parathyroid hormone; MDRD: modification of diet in renal disease.
All clinical and electrocardiographic variables were available for each patient. All biological variables were available, except for HbA1c, which was available only for the 25 diabetic patients (no diabetes was diagnosed during study), and iPTH (50 patients).

causes (10%). Renal biopsy was performed in 14 patients to confirm the type of nephropathy. Permanent AF was present in 10 patients (14%).

The echocardiographic findings are presented in Table 2. LVEF was < 50% in 10 patients (14%). Left ventricular hypertrophy (LVH), high left atrial surface area and elevated systolic pulmonary artery pressure were observed in 70%, 41% and 13% of patients, respectively. Finally, 26% of the population had a significantly reduced aortic valve area (< 1 cm^2/m^2).

During a mean follow-up of 258 ± 30 days, 18 patients (25%) reached the composite endpoint, 7 (10%) of whom died. All deaths were from cardiac or vascular causes (acute heart failure [$n=3$], mesenteric ischaemia [$n=3$] and ventricular fibrillation [$n=1$]). Fifty-one hospital admissions were documented in 32 patients, of which 57% were for cardiovascular causes. Nine patients began dialysis during follow-up (of whom two died during follow-up, two were transplanted and five were still undergoing dialysis at the end of follow-up). One patient underwent transplantation

Table 2 Echocardiographic characteristics of the study population.

	All ($n=71$)	Event-free ($n=53$)	Event ($n=18$)	P
Left ventricular ejection fraction (%)	62 ± 14	66 ± 11	52 ± 16	0.001
Indexed left ventricular mass (g/m^2)	133 ± 45	125 ± 43	158 ± 41	0.01
Left atrial surface area (cm^2)	19.2 ± 7.3	17.8 ± 5.6	23.2 ± 10.1	0.01
Aortic valve surface area (cm^2/m^2)	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.4	0.16
E mitral wave maximum velocity (cm/s)	77 ± 27	73 ± 23	90 ± 35	0.02
E mitral wave deceleration time (ms)	231 ± 84	235 ± 76	219 ± 105	0.52
Mitral E/A	0.91 ± 0.51	0.85 ± 0.35	1.15 ± 0.96	0.08
E/Ea	6.6 ± 2.4	6.4 ± 2.3	7.3 ± 2.7	0.18
IVRT (ms)	120 ± 29	120 ± 24	122 ± 40	NS
Systolic pulmonary artery pressure (mmHg)	34 ± 10	32 ± 6	39 ± 14	0.02

Data are presented as mean ± standard deviation. Ea: early peak velocity; IVRT: isovolumetric relaxation time; NS: not significant. Left ventricular mass was available for 68 patients (long axis parasternal view unusable in three patients). Left ventricular ejection fraction, left atrial surface area and data from transmitral flow were measurable in 69 patients. E/A ratio was not available in 11 patients (atrial fibrillation in all but one). Systolic pulmonary artery pressure was measured in 58 patients.

before dialysis could be initiated. Follow-up data and details of MACE are shown in Table 3.

Predictors of MACE

The comparison between patients who reached the composite endpoint and those who did not is presented in Tables 1 and 2.

By univariate analysis, there was no difference in age, history of atheromatous disease, traditional cardiovascular risk factors, causes of nephropathy, heart rate and blood pressure between the two groups. Patients who experienced MACE more often presented a history of acute heart failure ($P=0.02$) or diuretic treatment ($P<0.05$) and had a higher blood urea concentration ($P<0.01$). The dose of diuretics was higher in patients with MACE (93 ± 84 mg vs. 31 ± 48 mg of furosemide; $P<0.001$). We also noted a relation between blood urea and diuretic doses (24.8 ± 8.1 mmol/L for furosemide doses > 60 mg vs. 18.1 ± 5.7 mmol/L for furosemide doses < 60 mg [$P=0.002$] vs. 15.7 ± 5.7 mmol/L if no diuretic was prescribed [$P<0.0001$]). On electrocardiography and echocardiography, abnormal findings were more frequent in MACE patients: AF (44% vs. 4%), LVH (Sokolow index or left ventricular mass), increased left atrial surface area, protodiastolic transmitral flow peak, pulmonary artery pressure and decreased LVEF. Beta-blocker use was higher in the MACE group. Other medical therapy and biological and echocardiographic variables were not significantly different.

Among the 10 patients with AF, eight reached the composite endpoint (80%) compared with only 10 of the 61 (16%) patients in sinus rhythm ($P<0.01$).

By multivariable analysis of non-echocardiographic data, blood urea and AF were significantly associated with MACE, with an odds ratio (OR) of 1.13 (95% confidence interval [CI] 1.04—1.22) for an increase of 1 mmol/L in blood urea and an OR of 5.40 (95% CI 1.78—16.4) for AF.

By multivariable analysis of echocardiographic variables, LVEF with an OR of 0.95 (95% CI 0.91—0.99) and left atrial area with an OR 1.1 (95% CI 1.02—1.17) were found to be independently associated with cardiovascular events, an increase in LVEF having a protective effect. In the final multivariable analysis, which included both echographic and non-echographic variables significantly associated with MACE by univariate analysis, LVEF was the only echocardiographic factor independently associated with MACE (OR 0.93, 95% CI 0.89—0.97; $P<0.001$); among non-echocardiographic variables, only blood urea was significantly associated with MACE (OR 1.10, 95% CI 1.02—1.18; $P=0.002$).

In a post hoc analysis, when we set cut-off values for LVEF at 50% and blood urea at 15 mmol/L (corresponding to 2 × ULN), we found significant differences in the rate of MACE occurrence according to whether 0, 1 or 2 values were abnormal (Fig. 1). The association of LVEF > 50% and blood urea < 15 mmol/L had a negative predictive value of 95% for MACE occurrence, with a positive predictive value of 67% if both were abnormal (nine patients, of whom six presented with MACE).

Table 3 Events during follow-up.

Events	n (%)
All-cause deaths	7 (10)
Cardiovascular deaths	7 (10)
Cardiac and vascular events	18 (25)
Acute coronary syndromes	3 (4)
Ischaemic stroke	1 (1)
Acute mesenteric or peripheral artery ischaemia	5 (6)
Acute heart failure	12 (17)
Sustained ventricular arrhythmias	1 (1)
All-cause hospitalizations	32 (45)
End-stage renal disease	9 (13)
Pre-emptive kidney transplantation	1 (1)

Discussion

To the best of our knowledge, this is the first study to focus exclusively on patients with stage 4 CKD, assessing

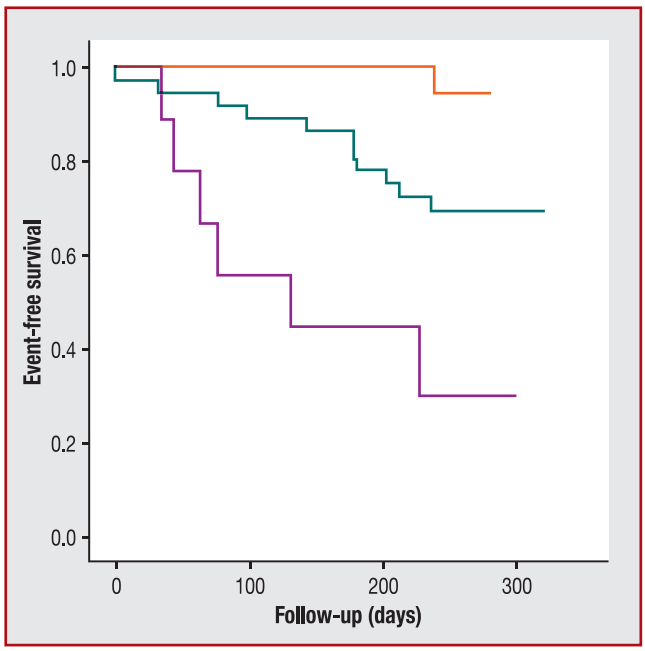

Figure 1. Kaplan-Meier curves representing cardiac and vascular event-free survival. LVEF: left ventricular ejection fraction. $P < 0.01$ by the log-rank test. LVEF > 50% and blood urea < 15 mmol/L ($n = 19$); LVEF ≤ 50% OR blood urea ≥ 15 mmol/L (not both) ($n = 36$); LVEF ≤ 50% and blood urea ≥ 15 mmol/L ($n = 9$).

both echocardiographic and non-echocardiographic predictors of MACE. Patients were selected according to estimated glomerular filtration rate, regardless of the origin of their nephropathy, clinical history and risk factors for CVD. Ninety-one percent of eligible stage 4 CKD patients were included and none was lost to follow-up. In contrast with other epidemiological studies [22], our population was predominantly male. However, sex was significantly (not independently) associated with MACE.

The prevalences of atheromatous disease and CVD risk factors were high in our study population, as reported in larger epidemiological studies [2,23,24], but these factors were also not shown to be associated with MACE.

We observed a high mortality rate; deaths were mostly related to cardiovascular causes. The occurrence of MACE, mainly acute heart failure, was frequent and was the leading cause of hospitalizations. These results are consistent with other epidemiological investigations [1,2,4,25]. Go et al. [2] found an annual mortality rate of 11.4%, with a cardiovascular event rate of 21.8% per year among stage 4 CKD patients. Indeed, CKD is known to be an independent risk factor for death and MACE [2,3,5,26,27].

Keith et al. found that 46% of a cohort monitored for 5.5 years died from CVD before reaching dialysis, while 20% needed dialysis or were transplanted by the end of the study [25]. Despite a shorter follow-up period in our study, MACE occurrence was more frequent than the need for renal replacement therapy.

Our study focused on echocardiographic evaluation. Few patients had systolic dysfunction. However, a lower LVEF was significantly associated with MACE occurrence and an increase of 1% in LVEF was associated with a 7% decrease in the risk of MACE. This association was independent of other variables, including left ventricular mass and left atrial size. These patients should benefit from the specific treatment recommended for patients with congestive cardiac failure and altered LVEF (namely angiotensin-converting enzyme inhibitors and beta-blockers), although their efficacy is less well established in severe CKD patients [16]. These results explain (in addition to using for AF rate control) the association of beta-blocker use with MACE (not confirmed in multivariable analysis). Among patients with LVEF < 50% ($n = 10$), five had previous documented coronary artery disease, two had normal coronary angiography and two had negative non-invasive evaluation of ischaemic risk. Low LVEF was previously shown to be an independent predictor of cardiovascular morbidity and mortality in asymptomatic dialysis patients [11] and of cardiovascular death in patients starting haemodialysis [9].

Congestive heart failure with preserved LVEF was probably due to diastolic dysfunction. Echocardiographic data favour this mechanism, as we found a significant association between several echocardiographic variables and MACE (left ventricular mass, left atrial size, systolic pulmonary arterial pressure and E mitral wave), all of which are altered in diastolic dysfunction [28]. Hayashi et al. showed that diastolic dysfunction is accentuated in patients with severe CKD and that echocardiography is useful in identifying it [29].

Left atrial size has been shown to be independently associated with cardiovascular mortality, regardless of whether patients required dialysis or had normal kidney function [30]. Moreover, left atrial dilatation promotes AF, a known risk factor for cardiovascular events in renal impairment [31,32] and, consequently, arterial thromboembolic complications. In our study, AF was significantly and independently associated with MACE occurrence by multivariable analysis of non-echocardiographic variables. AF has previously been identified as a risk factor for cardiovascular mortality among dialysis patients [31,32], mainly through the occurrence of fatal stroke, contrary to our patients in whom acute heart failure was more frequent. Indeed, in our final multivariable analysis, AF was not shown to be significantly related to MACE occurrence, mainly because, in our population, it was strongly associated with low ejection fraction and both are responsible for heart failure, which was the main cause of MACE. AF induces acute heart failure by decreasing systolic ejection volume (by loss of atrial systole and myocardial remodelling). Consequently, AF and decreased LVEF both contribute to MACE. Moreover, AF is frequently observed in diastolic dysfunction [28] and all these elements serve to underline the importance of diastolic dysfunction in these patients.

LVH was the most frequent abnormality observed on our echocardiographic data, as previously reported in many publications, ranging from 45% observed by Levin et al. among patients with creatinine clearance < 25 mL/min [33], to 66% in a report by Hayashi et al. [29]. LVH was significantly associated with the occurrence of MACE in our population. In addition, Sokolow LVH electrical index was also significantly associated with MACE. Silberberg et al. [7] was one of the first groups to show that LVH was an independent risk factor for CVD mortality in end-stage renal disease patients. In patients undergoing dialysis, Zoccali et al. reported that indexed left ventricular mass was associated with cardiovascular events, independent of traditional variables [10].

However, this relationship disappeared after adjustment for left ventricular systolic function [10], as also observed in our multivariable analysis.

Proteinuria has a significant impact on the decline of renal function [34] and an independent role on cardiovascular morbidity and mortality [35—37]. We did not observe a significantly higher level of proteinuria in the MACE group. Conversely, blood urea was significantly higher in the MACE group, whereas there was no significant difference in serum creatinine or estimated glomerular filtration rate between the two groups. There is a correlation between blood urea and protein carbamylation [38], but the impact of carbamylation on cardiovascular mortality is not clearly established. Nonetheless, as increased blood urea can be due to dehydration, we investigated ongoing diuretic treatment and found that higher doses of diuretics were being taken at the time of inclusion in the MACE group. Yet, diuretic treatment was not independently associated with MACE by multivariable analysis. It is likely that the MACE group required more diuretics to control fluid overload, while the increased blood urea level mirrored renal hypoperfusion. This was reflected in the blood urea-to-creatinine ratio, which was higher in the MACE group than in the MACE-free group.

Finally, combining LVEF and blood urea concentrations may help to predict MACE-free survival up to 1 year of follow-up. The association of an LVEF > 50% with blood urea < 15 mmol/L was associated in our study with low occurrence of MACE (5%) and was observed in 30% of our patients. The ability of these variables to positively predict MACE was lower but still useful in this population, with an estimated risk of 20—25% for MACE occurrence, with a positive predictive value of 67%.

Study strengths and limitations

The major strength of our study is the enrolment of stable stage 4 CKD patients, with regular follow-up in consultation, regardless of cardiovascular status.

The main limitations of our observational study were the small size of our cohort and the relatively short follow-up. Consequently, we were unable to analyse changes in LVH over time, or the impact of treatment modification. We also did not measure N-terminal pro-brain natriuretic peptide or cardiac troponin, which have been shown to be associated with cardiovascular mortality [39—41].

Conclusion

Stage 4 CKD patients have a greatly increased risk of MACE and premature cardiovascular death. While traditional risk factors are not associated with MACE in this specific population, LVEF and left atrial size were independent echocardiographic predictors of MACE. Finally, the association of LVEF > 50% with blood urea < 15 mmol/L had a high negative predictive value for MACE. In combination with increased blood urea concentrations, which reflect renal hypoperfusion and the kidney's inability to excrete sodium chloride, echocardiographic evaluation is probably effective for identifying at an earlier stage patients who could most benefit from optimized cardiac management.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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